**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

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| Appellants: | Jane C. Hirsh, Kamal K. Midha, Mark Hirsh, and Whe-Yong Lo | | |
| Serial No.: | 10/015,930 | Art Unit: | 1615 |
| Filed: | November 30, 2001 | Examiner: | Susan T. Tran |
| For: | *PHARMACEUTICAL COMPOSITIONS FOR COMPRESSED ANNULAR TABLET WITH MOLDED TRITURATE TABLET FOR BOTH INTRAORAL AND ORAL ADMINISTRATION* | | |

Assistant Commissioner for Patents
Washington, D.C. 20231

**APPEAL BRIEF**

Sir:

This is an appeal from the final rejection of claims 1-23 in the Office Action mailed September 12, 2003, in the above-identified patent application. A Notice of Appeal was mailed on January 29, 2004. An Amendment accompanies this Appeal Brief, along with a Petition for an Extension of Time for one month, up to and including April 28, 2004, and the appropriate fee.

The Commissioner is hereby authorized to charge $165.00 for the filing of this Appeal Brief, which is the appropriate fees for a small entity, to Deposit Order Account No. 50-1868. It is believed that no additional fee is required with this submission. However, should an additional fee be required, the Commissioner is hereby authorized to charge the fee to Deposit Account No. 50-1868.

## (1) REAL PARTY IN INTEREST

The real party in interest of this application is the assignee Peirce Management, LLC, Wellesley, MA.

## (2) RELATED APPEALS AND INTERFERENCES

There are no related appeals or interferences known to appellant, the undersigned, or appellant's assignee which directly affects, which would be directly affected by, or which would have a bearing on the Board's decision in this appeal.

## (3) STATUS OF CLAIMS ON APPEAL

Claims 1-23 are pending and on appeal.

## (4) STATUS OF AMENDMENTS

The claims were last amended in the amendment mailed on May 28, 2003. An amendment accompanies this appeal brief.

## (5) SUMMARY OF THE INVENTION

The claimed invention is the combination of (1) a triturate table containing a first drug with (2) a compressed annular tablet containing a second dose or a second drug (page 7, lines 23-24), where the triturate is molded around the compressed annular table (page 8, lines 1-3). Active ingredient for intraoral administration is contained in the triturate so that it is released rapidly when administered sublingularly (intraorally) (page 9, lines 20-23). The compressed annular tablet is then swallowed and the active ingredient released in the gut, either immediately or in a sustained or delayed release manner (page 9, lines 23-26).

## (6) ISSUES ON APPEAL

The issue presented on appeal is:

(a) whether claims 1-23 are obvious under 35 U.S.C. 103 over U.S. Patent No. 6,294,199 to Conley ("Conley").

## (8) ARGUMENTS

### (a) The Claimed Invention

The claimed invention is very specific: a two component delivery system, so that a first drug is administered rapidly in the mouth, and then a second dose or second drug is administered into the gut, where it is released immediately, in a sustained fashion, or delayed (such as with an enteric coating).

The benefits of this composition are principally in providing a single tablet for delivery of two drugs (or dosages) – one which is delivered immediately, and one later; and in avoiding first pass metabolism for the first drug delivered via the triturate. Intraoral administration also avoids problems with food interactions and stomach upset (page 10, lines 21-25). Ease of administration is particularly important for patient compliance in nursing homes and other institutions.

As discussed below, not all drugs are suitable for oral administration in a trituarate. The drugs need to be capable of being absorbed sublingually or buccally through the mucous membranes (page 11, lines 15-18). This typically requires the drugs be low molecular weight, and present in the formulation in an amount less than 30 mg (page 10, lines 1-5).

### (b) Rejection Under 35 U.S.C. § 103

*The Legal Standard*

The U.S. Patent and Trademark Office has the burden under 35 U.S.C. § 103 to establish a *prima facie* case of obviousness. *In re Warner et al.*, 379 F.2d 1011, 154

U.S.P.Q. 173, 177 (C.C.P.A. 1967), *In re Fine*, 837 F.2d 1071, 1074, 5 U.S.P.Q.2d 1596, 1598-99 (Fed. Cir. 1988). In rejecting a claim under 35 U.S.C. § 103, the Examiner must establish a *prima facie* case that: (i) the prior art suggests the claimed invention; and (ii) the prior art indicates that the invention would have a reasonable likelihood of success. *In re Dow Chemical Company*, 837 F.2d 469, 5 U.S.P.Q.2d 1529 (Fed. Cir. 1988).

The prior art must provide one of ordinary skill in the art with the motivation to make the proposed modifications needed to arrive at the claimed invention. *In re Geiger*, 815 F.2d 686, 2 U.S.P.Q.2d 1276 (Fed. Cir. 1987); *In re Lalu and Foulletier*, 747 F.2d 703, 705, 223 U.S.P.Q. 1257, 1258 (Fed. Cir. 1984). Claims for an invention are not *prima facie* obvious if the primary references do not suggest all elements of the claimed invention and the prior art does not suggest the modifications that would bring the primary references into conformity with the application claims. *In re Fritch*, 23 U.S.P.Q.2d, 1780 (Fed. Cir. 1992). *In re Laskowski*, 871 F.2d 115 (Fed. Cir. 1989). The Court of Appeals for the Federal Circuit warned that "the best defense against the subtle but powerful attraction of a hindsight-based obviousness analysis is rigorous application of the requirement for showing of the teaching or motivation to combine prior art references." *In re Dembiczak*, 175 F.3d 994 at 999 (Fed. Cir. 1999). The "question is whether there is something in the prior art as a whole to suggest the desirability, and thus the obviousness, of making the combination. *WMS Gaming, Inc. v International Game Technology*, 184 F.3d 1339 at 1355 (Fed. Cir. 1999). "[T]he showing must be clear and particular." *In re Dembiczak*, 175 F.3d 994 at 999 (Fed. Cir. 1999). Although with the answer in hand, the "solution" now appears obvious, that is not the test. The references

must themselves lead those in the art to what is claimed. And in this case, there is simply no such teaching.

*The Prior Art*

Claims 1-23 were rejected as obvious under 35 U.S.C. 103(a) over U.S. Patent No. 6,294,199 to Conley et al. ("Conley"). Conley describes a bilayer tablet containing an antibiotic, amoxycillin. The tablets contain a very large dosage, between 1900 and 2600 mg (col. 3, lines 36-38). The intent is to provide release in two doses (col. 3, lines 44-53). Note col. 7, lines 7-14, that says that the first dose is administered by oral ingestion, with release preferably within 30 minutes or an hour – definitely not immediate release in the oral cavity! This is what is meant by "immediate release". This is further emphasized by reference to the dosage at col. 7, lines 41-52, referring to dosages in the range of 100 mg of amoxycillin.

It is believed it would be helpful to respond first to some of the examiner's comments, in particular regarding Conley that "... language does suggest the active agent in the immediate release layer disintegrates rapidly in the mouth, and therefore, provide intraoral absorption". (see col. 8, lines 58-67). A clear distinction needs to be made between two different scenarios: (a) drug is released within the oral cavity and *absorbed within the oral cavity (intraoral absorption)* and (b) drug is released within the oral cavity, then swallowed with saliva, and finally *absorbed in the GI tract.* As discussed above, to be suitable for intraoral absorption drug needs to meet the following criteria:

molecular weight smaller than 350 daltons

small dose (up to 30-50 mg)

high and rapid aqueous solubility.

These are the features discussed in the applications as important to intraoral absorption. See page 10, lines 1-5; and page 11, lines 15-18, for example.

Amoxicillin is NOT suitable for intraoral administration since its molecular weight is above 350 (Mw of amoxicillin is 365.4) and is only slightly soluble in water (solubility is 4.0 mg/ml (see Merck Index, 12th Edition, MN 617)) and therefore not rapidly released. Additionally, due to amoxicillin pKa values (amine 7.49, COOH 2.68, and phenol OH 9.63), drug is absorbed most efficiently only after passing through the stomach and into the GI lumen having a pH 3-6 (above normal stomach pH), where the net charge of amoxicillin is zero (Nichols, W.K., Anti-Infectives. In: Gennaro, A.R. et al.: The Science and Practice of Pharmacy. 20th Edition. Baltimore: Lippincott, Williams, and Wilkens, 2000: 1520). No amoxicillin will be absorbed in the mouth since the oral cavity has a normal pH of 6.5. Moreover, the evidence that amoxicillin is not absorbed in the oral cavity is presented by Conley in Figure 3. $T_{max}$ of the various tested formulations of amoxicillin produced *in vivo* is between 1 and 2 hours, which is substantially higher than that of sublingually absorbed drugs ($T_{max}$ in the minute range). The therapeutic dose of amoxicillin is between 1900 and 2600 mg as described by Conley et al. (col. 8, lines 44-57; Claim 1 of US Patent No. 6,294,199), not less than 50 mg.

Conley does not make it obvious to a person ordinary skilled in the art to combine in one dosage form drugs for *intraoral* and *oral administration* since Conley does not describe an immediate release layer that dissolves intraorally to release amoxicillin for intraoral absorbtion.

Further, the active ingredients of appellants' claimed composition and method are systemically acting agents that are absorbed into the bloodstream at two different sites of

the human body: the first ingredient within the oral cavity and the second ingredient within the GI tract. Conley specifically states that "part of the challenge in providing formulations of amoxicillin ... is the relatively narrow window for **absorption of the drug in the small intestine**" (column 4, lines 33-37). Therefore, even if the composition described by Conley releases some amoxicillin in the mouth due to disintegration of the IR layer (column 11, lines 45-60) or when tablet is chewed (column 17, lines 25-65), the drug's absorption will occur in the small intestines, and it will not achieve meet the claimed limitations.

With respect to the method of claim 21, amoxicillin provides its therapeutic effect to the patient regardless of the way tablet is administered, i.e. swallowed, kept in the mouth and then swallowed, chewed and then swallowed, etc. In contrast, claim 21 requires the tablet be kept in the mouth until the intraoral portion is dissolved. This is essential or the dose of the drug intended for intraoral administration will not enter systemic circulation via transmucosal absorption in the oral cavity. Since most of the drugs intended for intraoral administration are unstable in the environment of the human GI tract (e.g. nitroglycerin), the patient will not benefit from the therapeutic effect of the intraoral drug if the tablet is swallowed without allowing the triturate to dissolve within the oral cavity.

With respect to claim 22, no where does Conley disclose a drug that has a problem with first pass metabolism, much less how to minimize this issue.

With respect to claim 23, Conley also fails to describe a drug which is capable of intraoral administration having a rapid onset through intraoral absorption.

In summary, Conley does not make obvious either the claimed formulation or method of manufacture or use, since Conley does not disclose the claimed features, in particular the features that provide for a triturate including a drug which is rapidly absorbed intraorally, nor the problems that would lead one to modify and combine the claimed features as appellants have done.

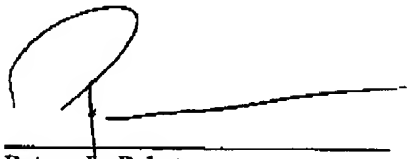
Moreover, Conley does not recognize the problems with the conventional delivery formulations that appellants address and solve. The claimed dosage form for intraoral/oral administration has advantages compared to conventional triturate tablets, which are fragile due to inherent softness. In the claimed intraoral/oral dosage form, the triturate portion in the center of the tablet is "protected" from mechanical damage by a surrounding layer of compressed tablet. The manufacturing process defined by claim 20 that is used to produce the intraoral/oral dosage form is different from that normally used to produce compressed conventional or bi-layer tablets. Conley completely fails to address these issues. Accordingly, Conley fails to make obvious the claimed method of manufacture.

## (9) SUMMARY AND CONCLUSION

In summary, none of the art motivates one skilled in the art to make a combination composition comprising a triturate containing a drug which is rapidly absorbed intraorally, molded around a compressed tablet containing drug which is release subsequently, typically after swallowing. Therefore the subject matter of claims 1-23 is not obvious.

For the foregoing reasons, Appellant submits that the claims 1-23 are patentable.

Respectfully submitted,



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**Appendix: Claims On Appeal**

1. (previously amended) A pharmaceutical composition in unit dosage form for both intraoral and oral administration to a patient which comprises:

(a) an intraorally releasing first portion, in the form of a molded triturate tablet comprising a therapeutically effective amount of at least one pharmaceutically active ingredient capable of intraoral administration; and

(b) a second releasing portion located around the first portion as a compressed annular tablet, comprising a therapeutic ingredient capable of oral administration and which is releasable and orally ingestible by the patient after the molded triturate has disintegrated or has dissolved intraorally.

2. ( cancel) The pharmaceutical composition defined in claim 1 in the form of a compressed annular tablet and a molded triturate tablet.

3. (original) The pharmaceutical composition defined in claim 1 wherein the compressed annular tablet is comprised of one or more layers containing the pharmaceutically active ingredient capable of oral administration.

4. (original) The pharmaceutical composition defined in claim 1 wherein the molded triturate tablet contains a therapeutically effective amount of at least one pharmaceutically active ingredient capable of intraoral administration and one or more pharmaceutically acceptable excipients for intraoral administration.

5. (original) The pharmaceutical composition defined in claim 2 wherein the molded triturate tablet is formulated with a pharmaceutically acceptable effervescent agent capable of generating effervescence when contacted with saliva.

6. (currently amended) The pharmaceutical composition as defined in claim 1 where the compressed annular tablet ~~may be~~ is film coated and ~~may contain~~ contains a pharmaceutically acceptable flavoring agent.

7. (original) The pharmaceutical composition defined in claim 3 wherein the compressed annular tablet is an immediate drug release tablet comprising at least one pharmaceutically active ingredient capable of oral administration and one or more pharmaceutically acceptable excipients for oral administration.

8. (original) The pharmaceutical composition defined in claim 3 wherein the compressed annular tablet comprises more than one layer including a sustained release layer containing a therapeutically effective amount of a first pharmaceutically active ingredient capable of oral administration and optionally including an immediate release layer containing a therapeutically effective amount of a second pharmaceutically active ingredient capable of oral administration, same or different from the first.

9. (original) The pharmaceutical composition defined in claim 3 wherein the compressed annular tablet comprises more than one layer comprising the pharmaceutically active ingredient capable of oral administration and where at least one of the layers comprising the pharmaceutically active ingredient capable of oral administration is an immediate drug release layer.

10. (original) The pharmaceutical composition defined in claim 8 where the compressed annular tablet provides sustained release of the pharmaceutical active ingredient capable of oral administration for a period of 0.5 to 24 hours.

11. (original) The pharmaceutical composition defined in claim 10 wherein the compressed annular tablet is formulated by incorporating or coating the pharmaceutically

active ingredient with one or more pharmaceutically acceptable sustained released polymers.

12. (original) The pharmaceutical composition defined in claim 11 wherein the one or more pharmaceutically acceptable sustained release polymer is selected from the group consisting of methylcellulose, hydroxypropyl methylcellulose, ethyl cellulose, cellulose acetate phthalate, acacia, gums, wax, glycerol monostearate, acrylic acid polymers and copolymers, methacrylic acid, methyl acrylate, ethyl acrylate, methyl methacrylate, ethyl methacrylate, and ion exchange resins capable of forming a sustained release ion-exchange resin-drug complex.

13. (original) The pharmaceutical composition defined in claim 3 wherein the compressed annular tablet comprises a therapeutically effective amount of one or more pharmaceutically active ingredients capable of oral administration in a delayed release form which delays the release of the one or more pharmaceutically active ingredients capable of oral administration for a period of 0.5 to 12 hours.

14. (currently amended) The pharmaceutical composition defined in claim 13 wherein the compressed annular tablet comprising a therapeutically effective amount of one or more pharmaceutically active ingredients capable of oral administration in a delayed release form includes a delayed release coating on the one or more pharmaceutically active ingredients, said delayed release coating comprising one or more pharmaceutically acceptable polymers selected from the group consisting of methylcellulose, hydroxypropyl methylcellulose, hydroxyethyl cellulose, hydroxymethyl cellulose, hydroxypropyl cellulose acetate succinate, ethyl cellulose, cellulose acetate phthalate, cellulose acetate trimellitate, carboxymethylcellulose sodium, acrylic acid

polymers and ~~copolymerss~~ copolymers, polymers or copolymers of methacrylic acid, methyl acrylate, ethyl acrylate, methyl methacrylate, ethyl methacrylate, vinyl acetate, vinyl acetate phthalate, an azo compound, polyvinyl pyrrolidone, pectin amylose, shelac, zein and guar gum.

15. (original) The pharmaceutical composition defined in claim 3 wherein the compressed annular tablet is chewable and comprises one or more pharmaceutically acceptable excipients suitable for a chewable medication and a flavoring agent.

16. (original) The pharmaceutical composition defined in claim 1 wherein the molded triturate tablet disintegrates or dissolves within 10 minutes permitting rapid release of the pharmaceutically active ingredient capable of intraoral administration, when the composition is contacted with saliva during intraoral administration.

17. (original) The pharmaceutical composition defined in claim 1 wherein the compressed annular tablet containing the pharmaceutically active ingredient capable of oral administration remains substantially intact until the intraoral administration of the pharmaceutically active ingredient capable of intraoral administration has been completed.

18. (original) The pharmaceutical composition defined in claim 1 wherein the pharmaceutically active ingredient capable of intraoral administration has a rapid onset of the desired therapeutic effect through intraoral absorption.

19. (original) The pharmaceutical composition defined in claim 1 wherein the pharmaceutically active ingredient capable of intraoral administration is selected from the group consisting of analgesics, antihistamines, antidiarrheal, anxiolytic, hypnotics, stimulants, cardiovascular drugs, pulmonary drugs, antihypertensives, antiemetics, anti-

inflammatory drugs, renal drugs, steroids, drugs fro neurological disorders, anti-psychotic drugs, drugs for treating endocrine disorders, drugs for promoting immunology, drugs for treating osteoarthritis, drugs for treating glaucoma, drugs for treating allergic rhinitis, drugs for treating anemias and other hematological disorders, drugs for treating infectious diseases, drugs for the treatment and symptoms of cancer, drugs for insomnia, and antidiabetic drugs.

20. (original) A process for the preparation of a pharmaceutical composition in unit dosage form as a compressed annular tablet with molded triturate tablet for both intraoral and oral administration to a patient, said pharmaceutical composition to be placed intraorally of said patient, which comprises:

(a) as a first releasing portion, a molded triturate tablet comprising a therapeutically effective amount of at least one pharmaceutically active ingredient capable of intraoral administration; and

(b) as a second releasing portion located around said first portion, a therapeutically effective amount of at least one pharmaceutically active ingredient capable of oral administration and which is releasable and orally ingestible by the patient after the inlaid triturate has disintegrated or has dissolved intraorally,

which comprises the steps of:

(i) providing the second portion as a single- or multi-layer compressed annular tablet, and

(ii) molding the first portion as a triturate tablet into the annulus of (i).

21. (original) A method of administering a pharmaceutical composition in unit dosage form as a compressed annular tablet molded triturate tablet for both intraoral and oral administration to a patient, which comprises:

(a) as a first releasing portion, a molded triturate tablet comprising a therapeutically effective amount of at least one pharmaceutically active ingredient capable of intraoral administration; and

(b) as a second releasing portion located around the said first portion, a therapeutically effective amount of at least one pharmaceutically active ingredient capable of oral administration and which is releasable and orally ingestible by the patient after the inlaid triturate has disintegrated or has dissolved intraorally, which comprises the steps of:

(i) placing the pharmaceutical composition under the tongue or against the inner wall of the cheek or within the vestibular mucosa of said patient;

(ii) retaining the pharmaceutical composition under the tongue or against the inner wall of the cheek or vestibular mucosa of the patient until the first releasing portion of the pharmaceutical composition containing the pharmaceutically active ingredient capable of intraoral administration has dissolved or has disintegrated thereby substantially releasing the pharmaceutically active ingredient capable of intraoral administration; and

(iii) following step (ii) sucking or swallowing whole or chewing and swallowing the second releasing portion of the pharmaceutical composition.

22. (original) The pharmaceutical composition defined in claim 1 wherein the pharmaceutically active ingredient capable of intraoral administration has a first pass metabolism which is avoided by intraoral administration.

23. (original) The pharmaceutical composition defined in claim 1 wherein the pharmaceutically active ingredient capable of intraoral administration has a rapid onset of desired therapeutic effect through intraoral absorption.

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